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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,676	10/29/2003	Keith L. Black	67789-503	8501

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EXAMINER

SCHNIZER, RICHARD A

ART UNIT PAPER NUMBER

1635

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/696,676

Applicant(s)

BLACK ET AL.

Examiner

Richard Schnizer, Ph. D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,110-200,204 and 205 is/are pending in the application.
- 4a) Of the above claim(s) 1,110-183,186,188-190 and 192-199 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 184, 185, 187, 191, 200, 204, and 205 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

An amendment was received and entered on 8/25/06.

Claims 201-203 were canceled and claims 204 and 205 were added as requested.

Claims 1, 110-200, 204 and 205 are pending.

Claims 1, 110-183, 186, 188-190, and 192-199 stand withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention or species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5/2/06.

Claims 184, 185, 187, 191, 200, 204, and 205 are under consideration in this Office Action. A species election applies to claims 184, 185, 187, and 191, i.e. the drug IL-2 was elected. Because these claims are rejected under 35 USC 112, first paragraph, search and examination has not been extended past the elected species.

Priority

Applicants amendment to the specification to clarify the priority claim is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 184, 185, 187, 191, and 200 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for calcium-activated potassium channel agonists such as NS-1619 and 1-EBIO, does not reasonably provide enablement for the use of a guanylyl cyclase activating protein as a calcium-activated potassium channel agonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims have been amended to recite that “guanylyl cyclase activating protein” is a calcium-activated potassium channel agonist. The specification as filed also implies that this is the case at page 10, lines 14-21. The claims as amended are not adequately enabled because the specification fails to teach how to use a guanylyl cyclase activating protein as a calcium-activated potassium channel agonist.

Robertson et al (Am. J. Physiol. 265 (1 pt 1): C299-303, 1993, of record) taught that cyclic GMP protein kinase (cGMP-PK) activates Ca-activated potassium channels (K_{Ca} channels) in cerebral artery smooth muscle cells. Therefore it is conceivable that activators of guanylate cyclase could indirectly act as K_{Ca} channel agonists by increasing intracellular cGMP and subsequently activating cGMP-PK. However, the prior art also taught that guanylyl cyclase activating proteins (GCAPs) interact with the intracellular domain of guanylyl cyclase, and not the extracellular domain. See e.g. Ermilov JBC 276(51): 48143-8 2001, abstract). Thus one of skill in the art would not expect that extracellular application of a GCAP, as envisioned in the specification, would result in activation of guanylyl cyclase. While the prior art taught K_{Ca} channel

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agonists that act extracellularly, such as bradykinin, NS-1619, and 1-EBIO, the prior art of record does not disclose the use of a GCAP to activate K_{Ca} channels by either an intracellular or extracellular mechanism. In the study of GCAP function, the prior generally taught the application of GCAPs to isolated membrane fractions that allow molecular access to either side of the membrane without need to enter a cell by traversing the membrane. See e.g. Ermilov (2001) paragraph bridging columns 1 and 2 on page 48144, Hwang et al (Biochem. 41:13021-13028, 2002) see paragraph bridging columns 1 and 2 on page 13022, or Frins et al (J. Biol. Chem. 271(14): 8022-8027, 1996) at page 8023, column 2, fifth full paragraph. There is no evidence of record that suggests, nor any reason to believe, that extracellularly administered GCAPS would activate a cellular guanylate cyclase because the intracellular guanylate cyclase domains with which GCAPS naturally interact would not be accessible to extracellularly administered GCAPs. Neither the specification nor the prior art of record provides any guidance or examples as to how one could induce cellular uptake of a GCAP to allow an extracellularly administered GCAP to interact with the appropriate intracellular guanylate cyclase domain such that guanylate cyclase is activated. Because GCAPS act intracellularly to activate guanylyl cyclases, one of skill in the art could not use them for their intended purpose of activating K_{Ca} channels absent some guidance as to how to cause them to be internalized into a cell. Absent such guidance, and in view of the state of the art, the level of unpredictability in the art, and the lack of working examples in the specification, the skilled artisan would have to perform undue experimentation in order to use a GCAP as a K_{Ca} channel agonist.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 200 and 205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Veltkamp et al (Stroke 29: 837-843, 1998).

Veltkamp taught methods of assaying the effects of NS-1619 on the vascular response to NMDA after hypoxia and ischemia. See abstract.

Veltkamp did not teach the organization of NS-1619 and NMDA into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

The text of Veltkamp, could be considered to be instructions for how to use the kit. However, it is noted that the "instructions for use" limitation does not receive patentable weight because the courts have repeatedly found that the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label

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on the product is immaterial so far as the question of patentability is concerned." The court in *In re Gulack* (217 USPQ 401 (1983)) found that printed matter has no patentable weight unless the printed matter affects the function of the product claimed. Also, see in *In re Ngai* (70 USPQ2D 1862 (2004)).

Claims 200 and 205 are rejected under 35 U.S.C. 103(a) as being unpatentable over Devor et al (Am. J. Physiol. 271(5): L775-84, 1996).

Devor evaluated the effects of 1-EBIO and charybdotoxin on chloride ion secretion in T84 monolayers. See abstract.

Devor did not teach the organization of 1-EBIO into a kit. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize these agents into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

The text of Devor could be considered to be instructions for how to use the kit. However, it is noted that the "instructions for use" limitation does not receive patentable weight because the courts have repeatedly found that the application of particular printed matter to an old article cannot render the article patentable. For example, in the Opinion Text of *In re Haller*, 73 USPQ 403 (CCPA 1947), the court stated "[w]hether the statement of intended use appears merely in the claim or in a label on the product is immaterial so far as the question of patentability is concerned." The court in *In re Gulack* (217 USPQ 401 (1983)) found that printed matter has no patentable weight

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unless the printed matter affects the function of the product claimed. Also, see in *In re Ngai* (70 USPQ2D 1862 (2004)).

Claim 204 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Black (US Patent 5,527,778) or Black (US Patent 5,434,137).

The '137 patent is drawn to methods of delivering a neuropharmaceutical or diagnostic agent to abnormal brain tissue by infusing bradykinin and simultaneously administering the neuropharmaceutical or diagnostic agent. See claims 3 and 6.

The '778 patent taught a method for introducing a neuropharmaceutical or neurodiagnostic agent into abnormal brain tissue present in a mammal, said method comprising the steps of infusing bradykinin or bradykinin analog into the carotid artery of said mammal, wherein said neuropharmaceutical agent is administered simultaneously with the infusion of bradykinin or bradykinin analog into said carotid artery. See e.g. claims 5-8.

The '137 and '778 patents do not explicitly disclose a composition comprising the bradykinin and the neuropharmaceutical or diagnostic agent. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to make a composition comprising both the bradykinin and the neuropharmaceutical or diagnostic agent in order to facilitate their simultaneous administration.

Response to Arguments

Applicant's arguments filed 8/25/06 have been fully considered but they are not persuasive.

Applicant argues at page 17 of the response that the rejections over Veltkamp and Devor are not appropriate because neither of these references teach the use of a kit or the components of a kit to deliver a medicant to an abnormal brain region. Regarding Veltkamp, Applicant argues essentially that NMDA is not a medicant because it is not listed in the instant specification as a medicant. This is unpersuasive because Applicant is arguing limitations that are not in the claims. The claims do not limit the nature of the medicant, and Applicant has presented no evidence or reason indicating that NMDA is not a medicant. With regard to the rejection over Devor, Applicant argues that charybdotoxin is an inhibitor of 1-EBIO which would defeat the purpose of administering 1-EBIO to the abnormal brain region. Again, Applicant's argument appears to be based on limitations that are not in the claims. The claims are to kits, not to methods. Whether or not one would administer 1-EBIO together with charybdotoxin is determinative of whether it would be obvious to include these reagents in a kit. Devor taught all of the components of the kits, Applicant has not shown otherwise. The question then is whether or not it would have been obvious to organize the components taught by Devor into a kit. Applicant has not directly addressed this issue. The Office holds that it would be obvious for the reasons given above, and the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 204 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,434,137.

Although the conflicting claims are not identical, they are not patentably distinct from each other.

The '137 patent is drawn to methods of delivering a neuropharmaceutical or diagnostic agent to abnormal brain tissue by infusing bradykinin and simultaneously administering the neuropharmaceutical or diagnostic agent. See claims 3 and 6.

The '137 patent does not explicitly claim a composition comprising the bradykinin and the neuropharmaceutical or diagnostic agent. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to make a

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composition comprising both the bradykinin and the neuropharmaceutical or diagnostic agent in order to facilitate their simultaneous administration.

Claim 204 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,527,778.

Although the conflicting claims are not identical, they are not patentably distinct from each other.

The '778 patent taught a method for introducing a neuropharmaceutical or neurodiagnostic agent into abnormal brain tissue present in a mammal, said method comprising the steps of infusing bradykinin or bradykinin analog into the carotid artery of said mammal, wherein said neuropharmaceutical agent is administered simultaneously with the infusion of bradykinin or bradykinin analog into said carotid artery. See e.g. claims 5-8.

The '778 patent does not explicitly disclose a composition comprising the bradykinin and the neuropharmaceutical or diagnostic agent. However, it would have been obvious to one of ordinary skill in the art at the time of the invention to make a composition comprising both the bradykinin and the neuropharmaceutical or diagnostic agent in order to facilitate their simultaneous administration.

Claim 204 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,043,223.

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Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claims 1-9 of the '223 patent are drawn to a pharmaceutical preparation comprising bradykinin or a bradykinin analog and a cyclic GMP specific phosphodiesterase inhibitor. Thus claims 1-9 anticipate and render obvious instant claim 204. Claims 11-20 of the '223 patent are drawn to methods of treating abnormal brain tissue by administration of bradykinin or a bradykinin analog and a cyclic GMP specific phosphodiesterase inhibitor. It would have been obvious to one of ordinary skill in the art at the time of the invention to make a composition comprising both the bradykinin and the neuropharmaceutical or diagnostic agent in order to facilitate their simultaneous administration, particularly in view of '223 claims 1-9.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

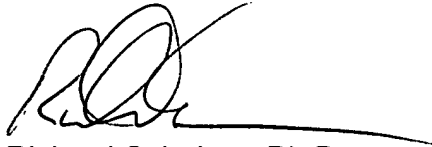
If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax

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number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

A handwritten signature in black ink, appearing to read 'Richard Schnizer', with a long horizontal line extending to the right.

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635